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CONSUMER PRODUCT SAFETY COMMISSION

16 CFR Part 1700

[Docket No. CPSC-2021-0027]

Poison Prevention Packaging Requirements; Proposed Exemption of Baloxavir Marboxil Tablets in Packages Containing Not More than 80 mg of the Drug

AGENCY: Consumer Product Safety Commission.

ACTION: Notice of Proposed Rulemaking.

SUMMARY: The Consumer Product Safety Commission (Commission or CPSC) is proposing to amend the child-resistant packaging requirements to exempt baloxavir marboxil tablets in packages containing not more than 80 mg of the drug, currently marketed as XOFLUZA,™ from the special packaging requirements. XOFLUZA is used to treat the flu, and is taken in one dose within 48 hours of experiencing flu symptoms. The proposed rule would exempt this prescription drug product on the basis that child-resistant packaging is not needed to protect young children from serious injury or illness because the product is not acutely toxic and lacks adverse human experience associated with ingestion.

DATES: Comments should be submitted no later than [**insert date 75 days after date of publication in the FEDERAL REGISTER**].

ADDRESSES: You may submit comments, identified by Docket No. CPSC- 2021-0027, by any of the following methods:

Electronic Submissions: Submit electronic comments to the Federal eRulemaking Portal at: https://www.regulations.gov. Follow the instructions for submitting comments. The CPSC does not accept comments submitted by electronic mail (e-mail), except through https://www.regulations.gov. The CPSC encourages you to

submit electronic comments by using the Federal eRulemaking Portal, as described above.

Mail/hand delivery/courier Written Submissions: Submit comments by mail/hand delivery/courier to: Division of the Secretariat, Consumer Product Safety Commission, 4330 East West Highway, Bethesda, MD 20814; telephone (301) 504-7479.

Instructions: All submissions received must include the agency name and docket number for this notice. All comments received may be posted without change, including any personal identifiers, contact information, or other personal information provided, to: https://www.regulations.gov. Do not submit electronically confidential business information, trade secret information, or other sensitive or protected information that you do not want to be available to the public. If you wish to submit such information please submit it according to the instructions for written submissions.

Docket: For access to the docket to read background documents or comments received, go to: https://www.regulations.gov, and insert the docket number, CPSC-2021-0027, into the "Search" box, and follow the prompts.

FOR FURTHER INFORMATION CONTACT: Cheryl A. Scorpio, Ph.D., Division of Pharmacology and Physiology Assessment, Directorate for Health Sciences, Consumer Product Safety Commission, 5 Research Place, Rockville, MD 20850; telephone (301) 987-2572; cscorpio@cpsc.gov.

SUPPLEMENTARY INFORMATION:

A. Background

1. *The Poison Prevention Packaging Act of 1970 and Implementing Regulations*

The Poison Prevention Packaging Act of 1970 (PPPA), 15 U.S.C. 1471–1476, gives the Commission authority to establish standards for the "special packaging" of household substances, such as drugs, when child-resistant (CR) packaging is necessary to protect children from serious personal injury or illness due to the substance, and the

special packaging is technically feasible, practicable, and appropriate for such substance. 15 U.S.C. 1472(a). Special packaging requirements under the PPPA have been codified at 16 CFR parts 1700 and 1702. Specifically, CPSC regulations require special packaging for oral prescription drugs. 16 CFR 1700.14(a)(10). CPSC regulations allow companies to petition the Commission for an exemption from CR requirements. 16 CFR Part 1702. Two "reasonable grounds"[1] for granting an exemption from the special packaging requirements are: (1) that the degree or nature of the hazard to children in the availability of the substance, by reason of its packaging, is such that special packaging is not required to protect children from serious personal injury or serious illness resulting from handling, using or ingesting the substance; or (2) special packing is not technically feasible, practicable, or appropriate for the subject substance. 16 CFR 1702.17(a) and (b).

If the Commission determines that reasonable grounds for an exemption are presented by a petition, CPSC regulations require publication in the *Federal Register* of a proposed amendment to the listing of substances that require special packaging, stating that the substance at issue is exempt. 16 CFR 1702.17.

2. *The Product for Which an Exemption Is Sought*

On March 30, 2020, Genentech, Inc. (Genentech), petitioned the Commission to exempt two specified sized tablets of baloxavir marboxil, which it markets as XOFLUZA from the special packaging requirements for oral prescription drugs. XOFLUZA was approved by the U.S. Food and Drug Administration (FDA) in October 2018, with a two-tablet dose for the acute uncomplicated flu in patients older than 12 years old showing symptoms for less than 48 hours. Single tablet doses have recently been approved by the FDA in March 2021. XOFLUZA has been marketed in tablet form and is currently

[1] A third reasonable ground for an exemption is that special packaging is incompatible with the particular substance. 16 CFR 1702.17(c). The petitioner has not requested an exemption on this basis so it is not relevant here.

dispensed in CR packaging. The petitioner asserted that an exemption from special packaging is justified because of the lack of toxicity and lack of adverse human experience with the drug. The petitioner also claimed that special packaging is not technically feasible, practicable, or appropriate for XOFLUZA. Staff's briefing memorandum provides a detailed assessment of the petitioner's claims regarding a request for an exemption from the special packing requirements for XOFLUZA. https://cpsc-d8-media-prod.s3.amazonaws.com/s3fs-public/Petition-to-Exempt-Baloxavir-Marboxil-XOFLUZA-in-40-mg-and-80-mg-Tablet-Doses-from-Special-Packaging-Requirements-of-the-PPPA-Cleared.pdf?VersionId=sLAhJ4THOBCtVMjgA4kxiFmI2.3LzqIj

B. Toxicity and Injury Data for XOFLUZA

Toxicity

CPSC staff reviewed the toxicity of XOFLUZA. XOFLUZA has been studied in pediatric patients (Hirotsu, 2019; Heo, 2018; NCT03653364, CAPSTONE 2; Hayden, 2018; Dziewiatkowski et al., 2019). Overall, clinically relevant doses of XOFLUZA (40 or 80 mg total dose) in humans are well tolerated (Dziewiatkowski et al., 2019; Taieb et al., 2019; Ng, 2019; Hayden, 2018).

The analysis of total adverse events (AE) included 10 studies with six treatments and 5628 patients. AE did not differ significantly between placebo and XOFLUZA. For drug-related vomiting, 3297 patients from five studies were included. XOFLUZA did not differ from placebo in these studies. (Taieb et al., 2019). The percentage of patients experiencing any adverse event[2] of 610 patients (12 to 64 years old) in the CAPSTONE 1 clinical trial was 1.0% grade 3 or grade 4, which can be categorized as not serious. Five

[2] The adverse events are: diarrhea, bronchitis, nasopharyngitis, nausea, sinusitis, increase in the level of AST, headache, vomiting, dizziness, leukopenia and constipation.

deaths have been reported by the AER System[3]; however, these deaths have been determined to not be related to XOFLUZA.

The most common AE of the correct dose of XOFLUZA was diarrhea (Heo, 2018; Shionogi prescribing info). The XOFLUZA Product Information, 2021 reported that diarrhea (3%), bronchitis (3%), nausea (2%), headache (1%) were the most significant adverse events found.

Treatment of an overdose of XOFLUZA should consist of general supportive measures, including monitoring of vital signs and observations of the clinical status of the patient. There is no specific antidote for overdose with XOFLUZA and it is unlikely to be significantly removed by dialysis because it is highly protein bound (Prescribing Information for XOFLUZA, 2021; Poisindex, 2021).

Overall, treatment with XOFLUZA is well tolerated. If accidentally ingested, the greatest potential for injury is diarrhea, nausea, and headache. For these reasons, CPSC staff determined that XOFLUZA will not cause serious injury or death upon acute exposure by a child under 5 years old.

Injury Data

CPSC staff searched the Consumer Product Safety Risk Management System (CPSRMS), the National Electronic Injury Surveillance System (NEISS) databases, and reviewed reports from FDA related to adverse events associated with XOFLUZA. CPSC staff found no incidents related to XOFLUZA in CPSRMS or NEISS from January 2015 through December 2020. CPSC staff also reviewed 12 reports received from FDA related to adverse events associated with XOFLUZA. Of the 12 reports, five involved XOFLUZA use only. Of these five incidents, two reported adverse effects. One patient

[3] The **Adverse Event Reporting System** (AERS) is a computerized information database designed to support the FDA's post-marketing safety surveillance program for all approved drug and therapeutic biologic products. The FDA uses AERS to monitor for new adverse events and medication errors that might occur with these marketed products.

experienced hallucination, fever, and sore throat, and the other patient suffered cardiac failure. Both were unrelated to XOFLUZA. Six incidents involved use of multiple drugs and were considered out of scope, and one was a duplicate.

C. Action on the Petition

After considering the information provided by the petitioner and other available toxicity and human experience data, the Commission concluded preliminarily that the "lack of toxicity and lack of adverse human experience for the substance" presented by the availability of 40 mg and 80 mg tablets of baloxavir marboxil (currently marketed as XOFLUZA) is such that special packaging is not required to protect children from serious injury or serious illness from handling, using, or ingesting XOFLUZA. 16 CFR 1702.17(a). Additionally, the Commission found that the petitioner's request for an exemption from special packaging, on the basis that it is not technically feasible, practicable, or appropriate for XOFLUZA, was not warranted based upon the information provided by the petitioner. Therefore, the Commission determined that reasonable grounds for an exemption were presented based on toxicity and voted to grant the petition and begin a rulemaking proceeding to exempt baloxavir marboxil tablets in packages containing not more than 80 mg of the drug from the special packaging requirements for oral prescription drugs.

Once the Commission determines that reasonable grounds for an exemption are presented by the petition, CPSC regulations require publication in the *Federal Register* of a proposed amendment to the listing of substances that require special packaging, stating that the substance at issue is exempt. 16 CFR 1702.17. This document proposes to amend the listing of substances in 16 CFR part 1700 that require special packing to state that baloxavir marboxil tablets in packages containing not more than 80 mg of the drug do not require special packing.

D. Description of the Proposed Rule

The proposed rule would amend 16 CFR part 1700 to include a new exemption from the special packaging requirements for baloxavir marboxil tablets in packages containing not more than 80 mg of the drug in proposed § 1700.14(a)(10)(xxiv). The proposed exemption is intended to cover baloxavir marboxil tablets for any dosage from 80 mg or below. The proposed rule would make no other changes to part 1700.

E. Regulatory Flexibility Act

Under the Regulatory Flexibility Act (RFA; 5 U.S.C. 601 et seq.), an agency that engages in rulemaking generally must prepare initial and final regulatory flexibility analyses describing the impact of the rule on small businesses and other small entities. Section 605 of the Act provides that an agency is not required to prepare a regulatory flexibility analysis if the head of an agency certifies that the rule will not have a significant economic impact on a substantial number of small entities.

CPSC staff prepared a preliminary assessment of the impact of the proposed rule to exempt baloxavir marboxil in 40 mg and 80 mg tablet form, currently marketed as XOFLUZA, from special packaging requirements. Genentech, Inc., is a subsidiary of, and owned in its entirety by the multinational corporation, Roche Group, the company that markets XOFLUZA. Roche Group employs 97,735 workers worldwide, of which 26,176 are located in North America. As of February 2020, Genentech employed 13,638 people. Roche Group's operating businesses are organized into two divisions: Pharmaceuticals and Diagnostics. Genentech, as the former third segment, has been integrated into Roche Pharmaceuticals. Sales in the Pharmaceuticals Division were $48.1 billion in 2019.

There are two main economic reasons for why granting the petition would not result in the exemption having a significant economic impact on a substantial number of small entities. First, the exemption for this drug is not likely to impact a large number of firms, therefore it is unlikely that granting the petition would impact a substantial number

of small entities. Second, CR packaging for XOFLUZA tablets is unlikely to be a significant amount of any firm's business, therefore granting the petition would not have a significant economic impact on any small entity. However, if the petitioner relocates packaging to another country, it could potentially result in some minor negative impacts for small domestic firms. Based on this assessment, we preliminarily conclude that the proposed amendment exempting baloxavir marboxil tablets in packages containing not more than 80 mg of the drug would not have a significant impact on a substantial number of small businesses or other small entities. We seek public comment on any small business impacts that might result from the exemption in the proposed rule.

F. Effective Date

The Administrative Procedure Act (APA) generally requires that a substantive rule must be published not less than 30 days before its effective date. 5 U.S.C. 553(d)(1). The NPR proposes an effective date of 30 days after publication of the final rule in the *Federal Register,* because the proposed rule would provide an exemption from the requirement to use special packaging for baloxavir marboxil tablets in packages containing not more than 80 mg of the drug.

G. Environmental Considerations

The Commission's regulations provide a categorical exclusion for the Commission's rules from any requirement to prepare an environmental assessment or an environmental impact statement where they "have little or no potential for affecting the human environment." 16 CFR 1021.5(c)(3). Rules exempting products from poison prevention packaging rules fall within the categorical exclusion, so no environmental assessment or environmental impact statement is required.

H. Preemption

The PPPA provides that, generally, when a special packaging standard issued under the PPPA is in effect, "no State or political subdivision thereof shall have any

authority either to establish or continue in effect, with respect to such household substance, any standard for special packaging (and any exemption therefrom and requirement related thereto) which is not identical to the [PPPA] standard." 15 U.S.C. 1476(a). A state or local standard may be excepted from this preemptive effect if: (1) the state or local standard provides a higher degree of protection from the risk of injury or illness than the PPPA standard; and (2) the state or political subdivision applies to the Commission for an exemption from the PPPA's preemption clause and the Commission grants the exemption through a process specified at 16 CFR part 1061. 15 U.S.C. 1476(c)(1). In addition, the federal government, or a state or local government, may establish and continue in effect a nonidentical special packaging requirement that provides a higher degree of protection than the PPPA requirement for a household substance for the federal, state, or local government's own use. 15 U.S.C. 1476(b).

Thus, with the exceptions noted above, the proposed rule exempting baloxavir marboxil tablets in packages containing not more than 80 mg of the drug from special packaging requirements, if finalized, would preempt nonidentical state or local special packaging standards for the substance.

List of Subjects in 16 CFR Part 1700

Consumer protection, Drugs, Infants and children, Packaging and containers, Poison prevention, Toxic substances.

For the reasons given above, the Commission proposes to amend 16 CFR part 1700 as follows:

PART 1700--[AMENDED]

1. The authority citation for part 1700 continues to read as follows:

Authority: 15 U.S.C. 1471–76. Secs. 1700.1 and 1700.14 also issued under 15 U.S.C.

2079(a).

2. Section 1700.14 is amended by adding paragraph (a)(10)(xxiv) to read as follows:

§ 1700.14 - Substances requiring special packaging.

(a) * * *

(10) * * *

(xxiv) Baloxavir marboxil tablets in packages containing not more than 80 mg of the drug.

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Alberta E. Mills, Secretary
U.S. Consumer Product Safety Commission

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